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Epithelioid sarcoma

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Abstract

Epithelioid sarcoma (ES) is a very rare sarcoma characterised by loss of INI-1. Enzinger first described ES in 1970, but the histopathologic differential diagnosis of ES remains challenging. There are two ES subtypes, the classical type with spindle epithelioid to central pseudogranulomatous cells, and the proximal type, which is predominantly composed of epithelioid and rhabdoid cells. ES symptoms and signs are not specific and depend on tumor localization. The only treatment for ES is radical excision with a microscope-radical margin. In general, the best treatment for ES in extremes is radical resecin with a wide margin or amputation with or without lymph node dissection. Surgery may be followed by adjuvant chemotherapy and/or radiation therapy. Referral of patients with ES to a sarcoma centre that offers hypofractionation RT trials and multidisciplinary clinical trials should be considered upfront. Neoadjuvant chemotherapy with ifosfamide and doxorubicin with / or without radiation therapy must be used after multidisciplinary team discussion. On 23 January 2020, the US Food and Drug Administration (FDA) first approved tazemetostat – an inhibitor of zeste homolog 2 Enhancer - therapy for metastatic ES or locally advanced ES not eligible for radical resection.

Key words: sarcoma, epithelioid sarcoma, Enzinger, tazemetostat

Introduction

Epithelioid sarcoma is a very rare (less than 1% of all soft tissue sarcomas) high-grade soft tissue sarcoma (STS) with a known propensity for locoregional recurrence and dissemination[1]. In general, ES tumours are built by spindled and epithelioid cells that circumscribe areas of central hyalinization and necrosis. Although ESs are of mesenchymal origin, their mixed differentiation makes their histopathological differential diagnosis challenging. The incidence in the EU and the United States is less than 0.2 and 0.5 new cases per million inhabitants per year, respectively. Enzinger first described epithelioid sarcoma (ES) in 1970 as a rare tumour of the distal extremities with epithelioid cytomorphology on pathological examination [2, 3]. The 5- and 10-year survival rates for ES are approximately 68% and 61%, respectively. No survival advantage was found for any gender, race, or

ethnic group [4]. In the course of the natural history of ES, local failure occurs in approximately 25%, lymph node involvement in 30% and distant metastases are found in more than 40% of patients [5]. However, ES is commonly initially diagnosed as a benign condition, thus delaying definitive treatment. ES it can also be misdiagnosed as another subtype of sarcoma:

- clear cell sarcoma,
- fibrosarcoma,
- synovial sarcoma,
- peripheral nerve sheath tumour,
- spinal cell sarcoma,
- fibrous histiocytosarcoma or other fibrohistiocytic tumour,
- nodular tenosynovitis or fasciitis,
- squamous cell carcinoma,
- Dupuytren's disease,
- necrotising granuloma,
- rheumatoid nodule [6, 7].

There are two typical ES morphologies:

- the classical type, which is a spindle-epithelioid to central pseudogranulomatous cells, and
- the proximal type, which is predominantly composed of epithelioid and rhabdoid cells.

Proximal ES is also known as the large cell subtype. The classic ES type is epidemiologically more common than the proximal type. Furthermore, the classic subtype is most commonly diagnosed in adolescents and young adults (10 to 40 years of age), while the proximal one in adults between 20 and 65 years of age. Classic ES is usually diagnosed in locations of the distal upper extremities with more than 50% developing in the hand and fingers. Proximal ESs develop more often in the hip, trunk, pelvis, peritoneal cavity, or inguinal and genital area. Proximal ES type is built of large cells with prominent nucleoli that resemble a poorly differentiated carcinoma and a frequent rhabdoid

phenotype. In ES, periosteal bone invasion may also occur, as well as central necrosis of the tumour, its haemorrhage or ulceration [8].

Epithelioid sarcoma symptoms and signs are not specific and depend on tumour location, therefore include lump or swelling area, with masses greater than 20 cm, slightly mobile tumours, painful on palpation and without skin changes, or ulcerated and indurated lesions, but also rectum bleeding, vaginal bleeding, epistaxis, hemoptysis, nausea, vomiting, abdominal pain, abdominal fullness, ptosis, headaches, neck pain, eye pain and swelling, diarrhoea or constipation, depression, anorexia, weight loss, or fever [2]. Regional spread of ES through lymphatic drainage and/or direct infiltration results in lymph node metastases, while distant metastases arise with hematogenous spread mainly in the lungs or liver [9]. Indolent tumour growth along with distal location may also lead to inappropriate primary diagnosis and subsequent surgical procedures prior to referral to the reference sarcoma clinic [10, 11]. Most often, at first, ES presents as a slowly growing, painless, and firm nodule, but the course of ES is unpredictable, including rapid progression with extensive lymph node or distant metastasis development. Furthermore, the natural history of ES is characterised by a high risk of multiple recurrences. ES tends to spread along the fascia and muscles, resulting in multifocality of the tumour [10, 12–14). The 5-year risk of recurrence after radical treatment is high, up to 70% [5, 13, 15, 16]. The ES tends to have regional lymphatic spread by more than 20% [6, 17, 18]. Patients with proximal-type tumour, ES tumour diameter >5 cm, multifocal tumours, nodal involvement, ES tumour necrosis, vascular invasion, and high mitotic index have shorter 5-year disease-specific survival (DSS) [14].

Epithelioid sarcoma has a complex genome with a high mutational rate that is comparable to that of ovarian carcinoma. More than 90% of ES cases are characterised by loss of function of integrase interactor 1 (*INI-1; SMARCB1/* hSNF5 – chromatin regulator, subfamily B, member 1 or malignant rhabdoid tumor suppressor) [11, 19]. The INI1 protein is a core component of the SWItch/ sucrose non-fermentable (SWI/SNF) chromatin remodelling complex that alters the structure of chromatin and facilitates transcription, replication, and DNA repair. INI1 is located on chromosome 22q11.2 [20]. Other key SWI/SNF complex subunits are BRG1 (SMARCA4), BRM (SNF2L2, SMARCA2), PBRM1 (hPB1, BAF180), and BAF155 (SMARCC1) that can all be lost in ES [21]. In ES, multiple mechanisms lead to inactivation of SMARCB1, including homozygous deletions, monoallelic deletion, nonsense point mutations, epigenetic mechanisms, and microRNA downregulation of mRNA [22]. INI1 signals regulate chromosomal stability by signaling *through* the p16INK4a-Rb-E2F pathway. At the same time in tumours with the *INI-1* gene, zeste homolog 2 (EZH2) signaling is up-regulated [23]. As a result, EZH2 is recruited to Polycomb targets and trimethylation of histone 3 lysine 27 in these

regions leads to repression of target genes [24]. The loss of INI1 expression is characteristic for both conventional ES and proximal ES [20].

Epithelioid sarcoma is characterised by the expression of carcinoma markers (e.g. cytokeratin and EMA) and sarcoma markers (e.g. vimentin), as well as CD34, while negative for: S-100, and CD31 [14]. Other alterations found in ES cells include activation of PI3K/AKT/mTOR, overexpression of EGFR, and activation of MET [11]. In an animal model, it was proven that smarcb1 deficiency with concordant *TP*53 mutation is sufficient to induce the development of ES [25]. In ES cells, it was shown that SMARCB1 negatively controls the expression of cyclin D1, E2F, and AURKA. As a result of the loss of SMARCB1 in these tumours, cyclin D1, E2F, and AURKA are upregulated and stimulate the cell cycle. In normal cells, SMARCB1/INI1 suppresses tumour progression by p16INK4a signaling to pRb (retinoblastoma), a tumour suppressor that negatively regulates cell cycle progression from G0/G1 to the S phase. At the same time, enhanced MYC activity and increased DNA replication are found in cells with SMARCB1 loss. Importantly, SMARCB1 interacts with the BRCA1, BARD1 and XPC proteins responsible for nucleotide excision repair. It also regulates chromosomal stability [26]. As a result, SMARCB1 loss results in fast proliferation of cells and mutation accumulation. SMARCB1 also inhibits the signaling of the sonic hedgehog (SHH) pathway, and this pathway is important in the development of radio and chemo-resistance [27, 28]. Next-generation sequencing (NGS) may enable further insights into the pathogenesis of ES, allow genetic classification, and biomarker discovery. NGS may also be used to verify the diagnosis [29, 30].

Radical treatment

The curative treatment of ES is radical excision with wide R0 margins. In general, the best treatment for ES in the extremities is *en bloc* excision. In cases with large tumours, amputation must often be performed in order to obtain radical resection with tumour-free margins. Primary tumour resection may be accompanied by lymph node dissection. After MDT adjuvant chemotherapy and/or radiation therapy can also be used in high-risk patients [31–33]. MDT should consider neoadjuvant chemotherapy for ES patients based on prognostic stratification with Sarculator nomogram for STS (https://www.sarculator.com/) [32, 34, 35].

The proximal subtype of ES is more aggressive, has higher rates of recurrence and metastases, and generally worse prognosis and higher mortality compared to classical ES [36]. In ES treatment, a sophisticated and well-planned surgical reconstruction can be performed with microsurgery, including free flap reconstruction or tendon transfers. In general practise, most ESs are

extracompartmental and infiltrate surrounding tissues, including the neurovascular plexus. Consequently, due to anatomical constraints, conservative surgery is not always possible in the case of locally advanced tumours. Furthermore, due to the common location in the distal part of the extremities, in cases of extensive infiltration of the soft tissues that limits the possibility of reconstruction, amputation can also be required [10, 12, 13]. In centrally located ES tumours, the complex anatomy surrounding the spine further complicates the treatment and often makes complete resection R0 extremely difficult or impossible [37]. If lymph node metastases occur, therapeutic lymph node dissection (LND) should be performed [6, 10, 38]. The high rate of nodal involvement may justify performing a sentinel node biopsy (SLNB) in selected cases of ES, but a low percentage of occult metastases was reported in this subtype of sarcoma. However, SLNB should be considered as a minimally invasive N disease staging procedure [17, 39–41].

Neodjuvant chemotherapy and radiotherapy (RT) can be considered in patients with ES after multidisciplinary team evaluation (MDT) [42]. In fact, radiation therapy has been reported to reduce the risk of local recurrence, but not overall survival (OS) [43]. At this point in time, radical surgery with conventionally fractionated perioperative RT is considered standard of care in ES [44], while patients should be referred to trials with RT hypofractionation and combined therapy clinical trials when available in a sarcoma centre. There are no phase III data on the role of RT in recurrent and metastatic ES. If RT was not used in radical treatment, perioperative RT may be considered in recurrent ES. In the event of a local recurrence in the field, re-irradiation should be considered only in selected cases. Patients with a limited volume of local ES recurrence can be treated with perioperative or definitive brachytherapy in sarcoma centres [45]. Select ES patients with oligometases may receive definitive radiation therapy [46, 47]. Patients with large recurrent ES tumours may receive multidisciplinary treatment with chemotherapy with RT with/without hyperthermia after MDT [48]. Palliative RT can be used for symptomatic ES metastases (palliative single fraction) [11].

In some cases, after MDT, perioperative chemotherapy can be considered [5, 13, 49, 50]. According to the current ESMO–EURACAN–GENTURIS Clinical Practise Guidelines, neoadjuvant treatment of operable localised STS of the extremities and the trunk wall is not yet standard treatment, although it can be proposed for fit patients with high-risk disease [51]. In patients with ES, MDT may advise perioperative chemotherapy for patients with large, high-grade tumours. After surgery with incomplete resection, as well as in the cases of up-front metastases, chemotherapy is also considered [42, 52]. In studies by NIO-PIB, Royal Marsden Hospital, Japan, and the French Sarcoma Group, doxorubicin with ifosfamide (AI) was the most commonly used [13, 49, 53, 54]. After neoadjuvant chemotherapy, objective and/or pathological responses are expected in 15% of cases

[13, 49, 55]. Chemotherapy regimens used in radical and / or first-line treatment should be based on doxorubicin. In addition to the AI regimen and doxorubicin monotherapy, the use of CyVADIC (cyclofosfamide, vincristine, doxorubicin, and dacarbazine) and VAIA (vincristine, doxorubicin, ifosfamide, actinomycin-D) were also been reported [11, 50]. Most recently, ES patients were recruited into a trial of radiation therapy with or without combination chemotherapy or pazopanib prior to surgery to treat patients with newly diagnosed nonrhabdomyosarcoma soft tissue sarcomas that can be removed by surgery. There are no reports on the association between perioperative chemotherapy and OS, DMFS, or LRFS [5, 42, 50, 52].

Systemic therapies in advanced epithelioid sarcoma

Epithelioid sarcoma metastasises most frequently to the lungs or pleura [6, 12, 15, 56]. High-risk epithelioid sarcomas are patients with large tumours, high tumour grade, inadequate tumour resection, and metastatic disease, predicting a relatively poor clinical outcome [57]. There are no specific guidelines based on high-quality evidence on systemic therapy in advanced ES [58]. Patients treated at Royal Marsden Hospital benefit from significantly longer OS when treated with palliative chemotherapy versus BSC (mOS: 16.8 *vs.* 8.7 months, p = 0.044) (50). Most available data on systemic ES therapy are reported as retrospective studies, case series, and case reports. Only a small number of patients with ES were treated in clinical trials. 27 ES patients were treated in EORTC trials 62012, 62043, 62072 and 62091. Among these cases, objective responses were reported for those treated with doxorubicin with ifosfamide (12.5 – 1/8), pazopanib (ORR 100% – 2/2), or trabectedin (33.3% – 1/3), but without OR when treated with doxorubicin monotherapy. The median PFS for patients treated first-line was 4.04 months. The median OS of these patients was only 10.93 months [59]. The analysis of 74 patients with ES has shown that patients receiving first-line systemic therapy have ORR of 15%, DCR of 20%, and a median DOR of 3.3 months (95% CI: 2.1– 5.2 months). In these patients, the mPFS was 2.5 months (95% CI: 1.7– 6.9 months), and the mOS was 15.2 months (95% CI: 11.4– 21.7 months). More than half of these patients were treated with regimens based on doxorubicin [60]. In general, the most extensive evidence on the use of chemotherapy in ES comes from a recently published series of 115 patients with advanced or metastatic ES. These patients were not treated with chemotherapy in a perioperative setting before treatment reported. This analysis has shown that there is no difference in response rates between patients treated with monotherapy anthracycline or with anthracycline combined with ifosfamide [61]. In clinical practise anthracyclines can be combined not only with ifosfamide, but also vincristine, dacarbazine, actinomycin D, cyclofosfamide, or carboplatin [38, 49, 50, 55, 62]. Anthracycline-based therapy results in favourable

disease control. In reported studies, ORR for anthracycline-based regimens is 22% (1 CR, 18 PR), while DCR – 75%. The response rate was numerically higher in proximal ES cases than in classical ES (26% *vs*. 19%, p = 0.44). The median PFS was 6.76 months (95%CI: 23–35). The median OS from the beginning of palliative chemotherapy was only 12 months (95% CI: 29–73). The six-month OS was 79% and the 12-month OS rate was 46% [49].

Another common regimen used in ES treatment is gemcitabine with docetaxel (GD) [50, 61, 63]. In 12 patients treated with gemcitabine-based chemotherapy, the ORR and DCR rates were 58% and 83%, respectively. When gemcitabine was used, the median PFS was 9 months in patients treated first-line and 8 months in the mixed population [63]. In another report on the use of gemcitabine in ES the ORR was reported to be 27%, while the DCR was reported to be 66% with the median PFS of 4 months. Interestingly, a trend toward higher response rates has been reported in the classical ES subtype (30% *vs*. 22%; p = 0.72) and the location of the distal tumour (40% *vs.* 14%; p = 0.08). No differences in ORR were reported between patients treated with gemcitabine monotherapy and GD chemoregimen [61]. Recently albumin-bound paclitaxel (nab-paclitaxel) 300 mg/m^2 via intravenous bolus on day 1, and gemcitabine 1250 mg/m^2 gemcitabine via intravenous bolus on days 1 and 8 chemoregimen was used in ES therapy and has been shown to be safe and moderately effective [64].

Only case reports on other chemotherapy agents in ES are published and include high-dose ifosfamide, trofosfamide, gemcitabine with cisplatin, dacarbazine, and trabectedin [63, 65]. An interesting case report was published showing complete remission (CR) of ES pulmonary metastases treated with vinorelbine (17–30 mg/m^2 every 2 to 4 weeks) therapy. In this case, the response CR was 4 years long [66]. Another ES case achieved a partial response (PR) with a duration of 27.4 months [67].

Targeted therapies for ES are still in development. **Pazopanib** is the first tyrosine kinase inhibitor (TKI) approved for ES therapy [50, 61]. In a case series of 18 pazopanib patients treated no ORRs were reported, 50% of the patients benefited with stable diseases (SD), but PFS was only 3 months. However, PR case reports on pazopanib treatment in patients with metastatic ES have also been published [68, 69]. In the pulled analysis of the EORTC trial, pazopanib was used in patients with ES in the second line and resulted in ORR 11.1% (1/9) and a median PFS of 2.73 months [59]. A case report on **sunitinib** therapy in ES was published. This patient achieved long-term stabilization of the disease (>32 months) after progression in two lines of chemotherapy [70]. Sunitinib in combination with nivolumab was found to improve PFS in patients with advanced epithelioid sarcoma [71].

Another therapy that has shown some benefit in case series is another TKI, anlotinib, in combination with PD-1 inhibitors [72]. Some data on **dasatinib** activity in ES are also available. In an

open-label single-arm SARC0009 study 2/7 patients achieved objective tumor responses according to Choi's criteria. The mPFS was 7.9 months and the PFS rate at 6 months was 57%. However, the OS was poor with a 2-year OS rate of 21% [73]. Another study investigates ipilimumab in combination with dasatinib in patients with refractory and/or unresectable GIST or other STS, including epithelioid sarcoma [74].

As ES sarcoma was reported to have a relatively high mutation rate, it is a candidate for **immune checkpoint inhibitor** therapies [75]. ES patient were recruited in a KEYNOTE-051 study of **pembrolizumab** in patients with PD-L1 positive, advanced, refractory, or refractory solid tumors, but no subgroup ORR was reported until now [76]. Case reports of the efficacy of pembrolizumab in advanced ES in adults have also been published. Pembrolizumab was used in the second line of palliative therapy, after chemotherapy with doxorubicin-ifosfamide [77]. In the study of **nivolumab**, a 24-year-old male ES metastatic lung patient had PR after 4 immunotherapy cycles, but the response was not durable as the patient progressed after the next 4 cycles [78]. An interesting case of long-term response to camrelizumab was recently published. This patient had high expression of PD-L1 and a high number of tumour-infiltrating lymphocytes in the tumour [79]. Currently, patients with ES are enroled in a study of nivolumab and ipilimumab in children and young adults with INI1 negative cancers and tigolumab and atezolizumab for the treatment of SMARCB1 or SMARCA4 deficient tumours.

On 23 January 2020, the US Food and Drug Administration (FDA) approved the first EZH2 methyltransferase **inhibitor** – **tazemetostat** – for the treatment of patients with locally advanced and metastatic epithelioid sarcoma not eligible for complete resection in patients older than 16 years. In a phase I trial (NCT02601937) with patients with tazemetostat ES, they achieved SD and continued treatment for >20 months [80]. Later, FDA approval was granted based on the results of a phase 2 trial (NCT02601950). In the analysed ES cohort (cohort 5) 62 patients were treated, 24 in the first line and 38 in the second or further lines. In the trial, patients were treated with 800 mg of tazemetostat twice daily. In the phase 2 trial, ORR was 15% (95% CI: 6.9–25.8), while DCR was 26% (95% CI: 15.5–38.5). In particular, ORR was 25% in patients treated in the first line, but only 8% in patients treated in other lines [81]. In this trial, 26% of the patients had disease control at 32 weeks and 21% remained progression-free at 1 year. The median response duration (DOR) was 16.1 months [82]. After FDA approval, the results of the treatment of patients from an additional cohort of ES (cohort 6) were reported. In cohort 6 ORR was 11.4% and DCR – 50% [82]. The final pooled analysis confirmed mPFS of 3.7 months and mOS – 18.0 months. The toxicity profile of tazemetostat is favourable. The most common AE are nausea and fatigue (in 40% of patients). Grade 3 treatment-related AEs were reported in 16% of the patients [81, 82]. Currently, in the next trial, tazemetostat is tested with

doxorubicin in the Phase 1b/3 trial as the first-line therapy for patients with advanced epithelioid sarcoma [83]. Furthermore, potential synergism between prior radiotherapy and TAZ requires further investigation [84]. A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma is ongoing [85]. ES patients are enroled in cohort D of the CAIRE: A multicenter open-label phase 2 basket study evaluating the EZH2 inhibitor tazemetostat in combination with durvalumab in patients with advanced solid tumours [86].

Conclusions

Epithelioid sarcoma is built by pleomorphic epithelioid cells and the proximal subtype is more aggressive than the classical subtype, as it has higher recurrence and metastasis rates, and shorter overall survival. ES occurs more frequently in adolescents and young adults with a slight predominance of men. Loss of expression of SWI/SNF chromatin-remodelling complex proteins plays an important role in ES development. At initial diagnosis, the tumour stage should be evaluated not only with clinical and radiological examination, but also with imaging focused on regional lymph nodes and the chest (pulmonary metastases). Surgical resection of primary tumours may be curative. The patient should be treated with wide local excision or with surgery plus lymphadenectomy. Radiation therapy should be considered after MDT to decrease the local recurrence rate. Currently hypofractionated preoperative RT may be advised [87, 88]. Referral to a sarcoma center for hypofractionated radiotherapy with hyperthermia may be considered in patients with marginally resectable or unresectable ES and in patients who are not eligible for chemotherapy [89]. Adjuvant radiation therapy is recommended in cases with positive margins (R1/R2 resections). Local recurrences are common in ES and most often develop within six months after radical treatment. Up to 75% of cases with local recurrence also develop distant metastases [9]. However, most patients have an advanced stage at first diagnosis with lymph node and / or lung metastases. Chemotherapy may provide palliation in patients with metastatic and unresectable epithelioid sarcoma, but responses are short and there is still an unmet need for more effective novel targeted therapies. Immunotherapy may be an alternative option for patients with metastatic ES. Most recently, tazemetostat showed activity in advanced ES with loss of INI1/*SMARCB1*. Tazemetostat therapy is a new treatment option for patients with ES approved by the FDA [90, 91].

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